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(54) Title: COSMETIC COMPOSITION CONTAINING CERAMIDE PRECURSORS

(57) Abstract

A composition for topical application to skin which comprises: (i) from 0.0001 to 10 % by weight of one or more ceramide pathway intermediates or precursors thereof and mixtures thereof; and (ii) a balancing amount of a cosmetically acceptable vehicle for the intermediate.

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COSMETIC COMPOSITION CONTAINING CERAMIDE PRECURSORS

FIELD OF THE INVENTION

The invention relates to skin-conditioning compositions and methods. It is particularly concerned with the stimulation of ceramide production in the epidermis, leading to an increase in the level of these lipid materials in the stratum corneum of the skin. The composition is also suitable for topical application to the hair and the nails.

BACKGROUND TO THE INVENTION

The stratum corneum, which is the outermost layer of the mammalian skin, contains intercellular lipids consisting predominantly of ceramides, cholesterol and fatty acids. From studies involving lipid depletion of the corneum by solvent extraction and from enzyme inhibition studies, ceramide in particular has been shown to be essential for the barrier function of the stratum corneum.

In normal skin, if there is perturbation of the barrier function, the epidermis normally re-synthesises the deficient lipids by inducing the expression or activation of the appropriate enzymes. However, under certain conditions, a reduced capacity for re-synthesis of the lipids may occur. This is especially so with elderly subjects, whose stratum corneum ceramide level is in any case reportedly lower than that of younger subjects.

The present invention is based upon the concept of stimulating the synthesis of ceramides in the epidermis by the topical application of precursors thereof in the biosynthetic pathway and/or by stimulation of the activity of enzymes responsible for catalysing the steps in the biosynthetic pathway that yields ceramide (as described later in this specification).

Synthesis of Ceramide

The synthesis of ceramide in the epidermis can be achieved by a variety of biochemical pathways, for example, those shown in Figure 1.

Common to each of these pathways are palmitoyl-CoA and serine, which are converted initially to 3-ketosphinganine in the presence of serine palmitoyl transferase. This is a rate limiting step and can accordingly adversely affect the rate of synthesis of ceramides via 3-ketosphinganine and the other intermediates as shown in these pathways.

We have now discovered that the rate of synthesis of ceramide in the epidermis can be increased following topical application of one or more intermediates in these biosynthetic pathways, especially those that are distal to the rate limiting step. We have also discovered that precursors comprising palmitoyl CoA and serine, can together increase ceramide synthesis, even though these are proximal to the rate limiting step.

The invention is accordingly concerned with the use of one or more of these ceramide pathway intermediates, following topical application, in enhancing the quality and condition of human skin, especially the water barrier properties thereof, in particular by increasing the rate of ceramide biosynthesis in the epidermis.

DEFINITION OF THE INVENTION

According to the invention, there is provided a composition suitable for topical application to human skin which comprises:

(i) from 0.0001 to 10% by weight of a ceramide pathway intermediate or a precursor thereof or mixtures thereof;

and

(ii) a balancing amount of a cosmetically acceptable vehicle for the ceramide pathway intermediate or precursor thereof.

The invention is also concerned with a method of treating skin, particularly dry and aged skin, with topically applied ceramide pathway intermediate, or a precursor thereof or mixtures thereof, in order to maintain or repair the skin barrier which controls moisture loss from the skin.

The invention is also concerned with the use of one or more ceramide pathway intermediates, or precursors thereof or mixtures thereof in maintaining or enhancing the skin barrier function which controls moisture loss from the skin and in the treatment of skin to reduce or delay the development of wrinkles associated with advancing age, or with sun-induced skin ageing.

The invention is also concerned with the use of at least 0.0001% by weight based on the total composition, of a ceramide pathway intermediate in a composition suitable for topical application to human skin comprising a major proportion of a cosmetically acceptable vehicle for the ceramide pathway intermediate.

DISCLOSURE OF THE COMPOSITION OF THE INVENTION

The composition according to the invention comprises in its simplest form a ceramide pathway intermediate or a precursor thereof, or mixtures thereof together with a cosmetically acceptable vehicle, the composition being suited for topical application to human skin.

The primary function of the said intermediate or precursor

thereof is to stimulate the synthesis of ceramide in the epidermis which then leads to higher ceramide levels in the stratum corneum. The water permeability barrier function of the skin, is thereby improved and the ability of the skin to retain moisture consequently enhanced.

The consumer perceived benefits that accordingly accrue from higher levels of ceramide in the stratum corneum achieved in this way are to be seen in the improvement in skin condition, such as eradication or reversal of skin ageing, including removal of age spots, keratoses, wrinkles, skin lines, blotches, blemishes, nodules, pigmented spots, coarse, rough and dry skin, together with improvements in skin barrier function leading to fewer problems of skin sensitivity, photodamaged skin, loss of elasticity and flexibility.

The Ceramide Pathways

With reference to Figure 1, which shows three alternative biosynthetic pathways for the production of ceramides in human skin, it can be seen that each has a common rate limiting step, namely the conversion of palmitoyl-CoA and serine to 3-ketosphinganine in the presence of serine palmitoyltransferase.

With reference to Ceramide Pathway I (Figure 1), 3-ketosphinganine is then converted to sphinganine in the presence of NADPH-dependant reductase and final conversion to Ceramide(A), via sphinganine in the presence of fatty acyl-CoA.

With reference to Ceramide Pathway II, 3-ketosphingosine is converted firstly to sphinganine and then secondly to sphingosine, and then to N-acyl sphingosine (Ceramide (B)).

With reference to Ceramide Pathway III, 3-ketosphinganine is converted to sphinganine in the presence of NADPH-dependant reductase, as occurs in Ceramide Pathway I, but then sphinganine is converted firstly to sphingosine, and secondly to phytosphingosine and then to N-acylphytosphingosine (Ceramide (C)).

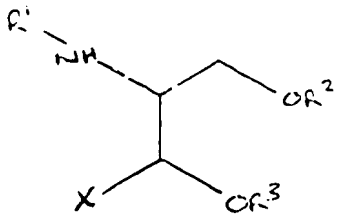
The Ceramides produced via ceramide pathways I, II and III are likely to be structurally different from each other and for this purpose are designated Ceramides (A), (B) and (C).

It is to be understood that the above ceramide pathways are purely illustrative and do not represent the only pathways available for the production of ceramide.

The Ceramide Pathway Intermediates

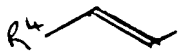
As has been explained, the conversion of palmitoyl-CoA and serine to 3-ketosphinganine in the presence of serine palmitoyltransferase represents the rate limiting step, ie the step which limits the formation of ceramide in the skin and other tissues. Accordingly, in order to enhance the rate at which ceramide is formed, particularly in the skin, it is preferred to deliver to the skin an effective amount of a precursor of ceramide which enters one or more of the Ceramide Pathways distal to this rate limiting step.

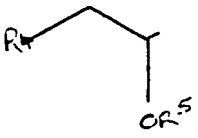
The rate of formation of ceramide can thus be enhanced by providing as precursors sphingoid bases, typical examples of which are sphinganine, sphingosine and phytosphingosine and derivatives thereof in accordance with structure (1):

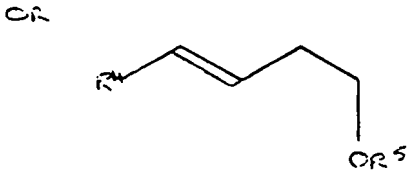


(1)

where X is represented by







and where R^1, R^2, R^3 and R^5 are each individually represented by H-, $CH_3(CH_2)_n$-

$CH_3(CH_2)_n(CHOH)_n$-, $CH_3(CH_2)_n(CHOH)_nC(=O)$- or

$CH_3(CH_2)_nC(=O)$-,

or phosphorylated, sulphated, glycosylated and benzoyl derivatives thereof;

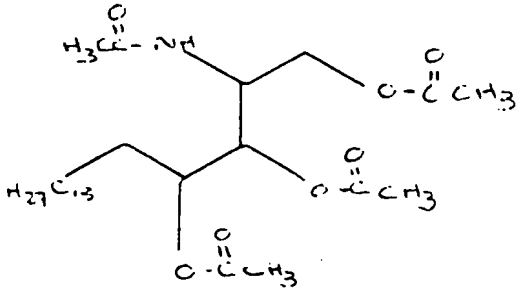
where n is O, or an integer of from 1 to 10, and

R^4 is $CH_3(CH_2)_m$ -

where m is an integer of from 1 to 21.

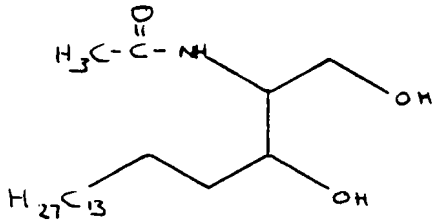
One preferred group of ceramide pathway intermediates includes: sphinganine, sphingosine and phytosphingosine and their respective N-acyl, O-acyl and N-alkyl derivatives.

A particularly preferred ceramide pathway intermediate is tetraacetyl phytosphingosine having the structure (2):



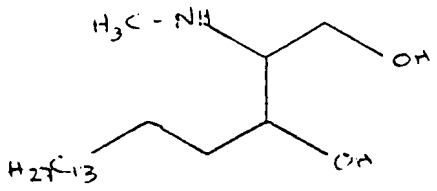
(2)

Particularly preferred derivatives of sphinganine are N-acetyl sphinganine having the structure (3):



(3)

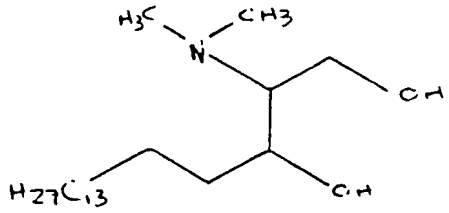
N-methyl sphinganine having the structure (4):



(4)

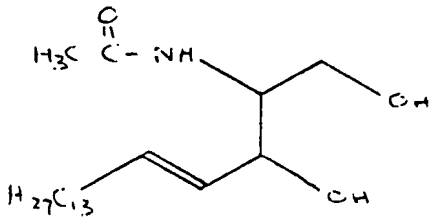
The acyl substituent is suitably a C_{1-16} acyl group preferably acetoxy. Conveniently, the pathway intermediate may be acylated at teh N-atom and one or more of hte oxygen atom present. The alkyl substituent is suitably C_{1-16}, preferably C_{1-4}, especially methyl. The nitrogen atom may be mono- or di-alkylated.

N,N^1-dimethylsphinganine having the structure (5):



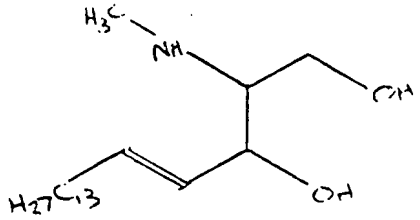
(5)

Particular preferred derivatives of sphingosine are -acetylsphingosine having the structure (6):



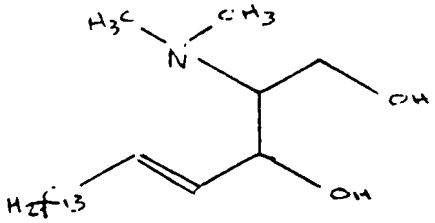
(6)

N-methyl sphingosine having the structure (7):



(7)

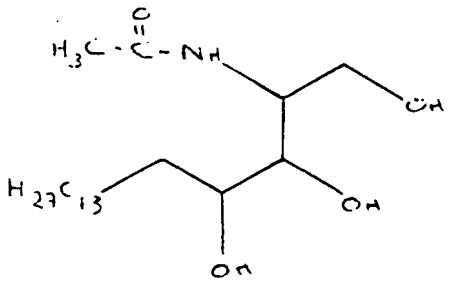
N,N^1-dimethylsphingosine having the structure (8):



(8)

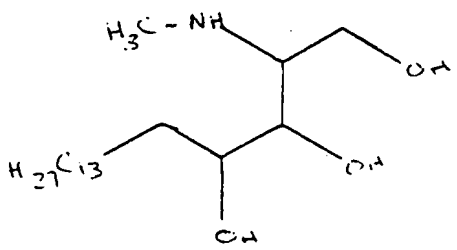
Other particularly preferred derivatives of phytosphingosine are:

N-acetylphytosphingosine having the structure (9):



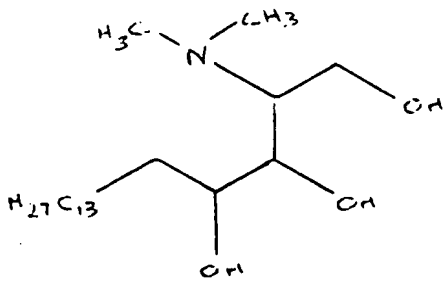
(9)

N-methyl phytosphingosine having the structure (10):



(10)

and N,N^1 dimethyl phytosphingosine having the structure (11):



(11)

It is to be understood that the above structures (2) to (11) are illustrative of derivatives of ceramide pathway intermediates which are useful in accordance with the invention and that there are many other derivatives that fit structure (1) that are also useful.

As has been explained earlier, it is also possible to employ precursors of ceramide synthesis that occur proximal to the rate limiting step in the ceramide pathway. These precursors are preferably palmitoyl CoA and serine which together are converted to 3-ketosphinganane by the enzyme serine palmitoyltransferase.

The amount of a selected ceramide pathway intermediate including precursors thereof or mixture thereof that should be incorporated in the composition according to the invention is from 0.0001 to 10%, preferably from 0.1 to 5% and ideally from 0.05 to 2% by weight of the composition.

THE COSMETICALLY ACCEPTABLE VEHICLE

The composition according to the invention also comprises a solid, semi-solid or liquid cosmetically and/or physiologically acceptable vehicle, to enable the ceramide pathway intermediate to be conveyed to the skin at an appropriate dilution. The nature of the vehicle will depend upon the method chosen for topical administration of the composition. The vehicle can itself be inert or it can possess physiological or pharmaceutical benefits of its own.

The selection of a vehicle for this purpose presents a wide range of possibilities depending on the required product form of the composition. Suitable vehicles can be classified as described hereinafter.

It should be explained that vehicles are substances which can act as diluents, dispersants, or solvents for the ceramide pathway intermediate which therefore ensure that they can be applied to and distributed evenly over the skin, hair or nails at an appropriate concentration. The vehicle is preferably one which can aid penetration of the ceramide pathway intermediate into the skin to enable it more readily to influence the skin condition.

Compositions according to the invention can include water as a vehicle, and/or at least one cosmetically acceptable vehicle other than water.

Vehicles other than water can include liquid or solid emollients, solvents, humectants, thickeners and powders. Examples of each of these types of vehicle, which can be used singly or as mixtures of one or more vehicles, are as follows:

Emollients, such as stearyl alcohol, glyceryl

monoricinoleate, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, eicosanyl alcohol, behenyl alcohol, cetyl palmitate, silicone oils such as dimethylpolysiloxane, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, cocoa butter, corn oil, cotton seed oil, olive oil, palm kernel oil, rapeseed oil, safflower seed oil, evening primrose oil, soybean oil, sunflower seed oil, avocado oil, sesame seed oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum jelly, mineral oil, squalane, squalene, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate;

Propellants, such as propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide;

Solvents, such as ethyl alcohol, methylene chloride, isopropanol, acetone, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran;

Powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silica sodium polyacrylate, tetra alkyl and/or trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, ethylene glycol distearate;

The cosmetically acceptable vehicle will usually form from

10 to 99.999%, preferably from 10 to 99% and most preferably from 50 to 99% by weight of the composition, and can, in the absence of other cosmetic adjuncts, form the balance of the composition.

Ceramide Pathway Adjuncts

In the biosynthesis of ceramide as hereinbefore described, the provision of ceramide pathway adjuncts in the composition according to the invention is preferable.

For example, the ceramide pathway intermediates and precursors thereof are preferably accompanied by saturated or unsaturated, straight or branched chain fatty acids or their esters, particularly their coenzyme A derivatives, or adenosine monophosphate derivatives, or preferably alpha-, beta or omega hydroxylated straight or branched chain fatty acids and esters thereof, especially the omega hydroxy linoleoyl ester.

The amount of selected ceramide pathway adjuncts, when employed, can be similar to that of the ceramide pathway intermediate or precursor thereof.

OPTIONAL SKIN BENEFIT MATERIALS AND COSMETIC ADJUNCTS

Penetration Enhancer

The composition according to the invention can also optionally comprise a penetration enhancer which can potentiate the benefit of the ceramide pathway intermediate or precursor thereof by improving its delivery through the stratum corneum to its site of action in the epidermis.

The penetration enhancer can accordingly function in a variety of ways. It can for example, improve the distribution of the ceramide pathway intermediate on the

skin surface or, it can increase its partition into the skin from the composition when applied topically, so aiding its passage to its site of action. Other mechanisms enhancing the benefit of the ceramide pathway intermediate may also be involved.

Examples of penetration enhancers include:

2-methyl propan-2-ol
Propan-2-ol
Ethyl-2-hydroxypropanoate
Hexan-2,5-diol
POE(2) ethyl ether
Di(2-hydroxypropyl) ether
Pentan-2,4-diol
Acetone
POE(2) methyl ether
2-hydroxypropionic acid
2-hydroxyoctanoic acid
Propan-1-ol
1,4 Dioxane
Tetrahydrofuran
Butan-1,4-diol
Propylene glycol dipelargonate
Polyoxypropylene 15 stearyl ether
Octyl alcohol
POE ester of oleyl alcohol
Oleyl alcohol
Lauryl alcohol
Dioctyl adipate
Dicapryl adipate
Diisopropyl adipate
Diisopropyl sebacate
Dibutyl sebacate
Diethyl sebacate
Dimethyl sebacate
Dioctyl sebacate

Dibutyl suberate
Dioctyl azelate
Dibenzyl sebacate
Dibutyl phthalate
Dibutyl azelate
Ethyl myristate
Dimethyl azelate
Butyl myristate
Dibutyl succinate
Didecyl phthalate
Decyl oleate
Ethyl caproate
Ethyl salicylate
Isopropyl palmitate
Ethyl laurate
2-ethyl-hexyl pelargonate
Isopropyl isostearate
Butyl laurate
Benzyl benzoate
Butyl benzoate
Hexyl laurate
Ethyl caprate
Ethyl caprylate
Butyl stearate
Benzyl salicylate
Dimethyl sulphoxide
N,N-Dimethyl acetamide
N,N-Dimethyl formamide
2-Pyrrolidone
1-Methyl-2-pyrrolidone
5-Methyl-2-pyrrolidone
1,5-Dimethyl-2-pyrrolidone
1-Ethyl-2-pyrrolidone
Phosphine oxides
Sugar esters
Tetrahydrofurfural alcohol
Urea

Diethyl-m-toluamide, and
1-Dodecylazacycloheptan-2-one

The amount of penetration enhancer, when employed in accordance with the invention, will normally be from 0.1 to 50%, preferably from 0.5 to 25% and most preferably from 0.5 to 10% by weight of the composition.

A particularly convenient form of the composition according to the invention is an emulsion, in which case an oil or oily material will normally be present, together with an emulsifier to provide either a water-in-oil emulsion or an oil-in-water emulsion, depending largely on the average hydrophillic-lyophilic balance (HLB) of the emulsifier employed.

Oil or Oily Material

The composition according to the invention can optionally comprise one or more oils or other materials having the properties of an oil.

Examples of suitable oils include mineral oil and vegetable oils, and oil materials, such as those already proposed herein as emollients. Other oils or oily materials include silicone oils, both volatile and non-volatile, such as polydimethyl siloxanes.

The oil or oily material, when present for the purposes for forming an emulsion, will normally form up to 90%, preferably from 10 to 80% by volume of the composition.

Emulsifier

The composition according to the invention can also optionally comprise one or more emulsifiers the choice of which will normally determine whether a water-in-oil or

and oil-in-water emulsion is formed.

When a water-in-oil emulsion is required, the chosen emulsifier or emulsifiers should normally have an average HLB value of from 1 to 6. When an oil-in-water emulsion is required, a chosen emulsifier or emulsifiers should have an average HLB value of >6.

Examples of suitable emulsifiers are set below in Table 1 in which the chemical name of the emulsifiers is given together with an example of a trade name as commercially available, and the average HLB value.

TABLE 1

Chemical Name of Emulsifier	Trade Name	HLB Value
Sorbitan trioleate	Arlacel 85	1.8
Sorbitan tristearate	Span 65	2.1
Glycerol monooleate	Aldo MD	2.7
Glycerol monostearate	Atmul 84S	2.8
Glycerol monolaurate	Aldo MC	3.3
Sorbitan sesquioleate	Arlacel 83	3.7
Sorbitan monooleate	Arlacel 80	4.3
Sorbitan monostearate	Span 60	4.7
Poloxyethylene (2) stearyl ether	Brij 72	4.9
Poloxyethylene sorbitol beeswax derivative	G-1702	5
PEG 200 dilaurate	Emerest 2622	6.3
Sorbitan monopalmitate	Arlacel 40	6.7
Polyoxyethylene (3.5) nonyl phenol	Emulgen 903	7.8
PEG 200 monostearate	Tegester PEG 200 MS	8.5

Sorbitan monolaurate	Arlacel 200	8.6
PEG 400 dioleate	Tegester PEG 400-DO	8.8
Polyoxyethylene (5) monostearate	Ethofat 60-16	9.0
Polyoxyethylene (4) sorbitan monostearate	Tween 61	9.6
Polyoxyethylene (4) lauryl ether	Brij 30	9.7
Polyoxyethylene (5) sorbitan monooleate	Tween 81	10.0
PEG 300 monooleate	Neutronyx 834	10.4
Polyoxyethylene (20) sorbitan tristearate	Tween 65	10.5
Polyoxyethylene (20) sorbitan trioleate	Tween 85	11.0
Polyoxyethylene (8) monostearate	Myrj 45	11.1
PEG 400 monooleate	Emerest 2646	11.7
PEG 400 monostearate	Tegester PEG 400	11.9
Polyoxyethylene 10 monooleate	Ethofat 0/20	12.2
Polyoxyethylene (10) stearyl ether	Brij 76	12.4
Polyoxyethylene (10) cetyl ether	Brij 56	12.9
Polyoxyethylene (9.3) octyl phenol	Triton X-100	13.0
Polyoxyethylene (4) sorbitan monolaurate	Tween 21	13.3
PEG 600 monooleate	Emerest 2660	13.7
PEG 1000 dilaurate	Kessco	13.9
Polyoxyethylene sorbitol lanolin derivative	G-1441	14.0
Polyoxyethylene (12) lauryl ether	Ethosperse LA-12	14.4
PEG 1500 dioleate	Pegosperse 1500	14.6

Polyoxyethylene (14) laurate	Arosurf HFL-714	14.8
Polyoxyethylene (20) sorbitan monostearate	Tween 60	14.9
Polyoxyethylene 20 sorbitan monooleate	Tween 80	15.0
Polyoxyethylene (20) stearate	Myrj 49	15.0
Polyoxyethylene (20) stearyl ether	Brij 78	15.3
Polyoxyethylene (20) sorbitan monopalmitate	Tween 40	15.6
Polyoxyethylene (20) cetyl ether	Brij 58	15.7
Polyoxyethylene (25) oxypropylene monostearate	G-2162	16.0
Polyoxyethylene (20) sorbitol monolaurate	Tween 20	16.7
Polyoxyethylene (23) lauryl ether	Brij 35	16.9
Polyoxyethylene (50) monostearate	Myrj 53	17.9
PEG 4000 monostearate	Pegosperse 4000 MS	18.7

The foregoing list of emulsifiers is not intended to be limiting and merely exemplifies selected emulsifiers which are suitable for use in accordance with the invention.

It is to be understood that two or more emulsifiers can be employed if desired.

The amount of emulsifier or mixtures thereof, to be incorporated in the composition of the invention, when

appropriate is from 1 to 50%, preferably from 2 to 20% and most preferably from 2 to 10% by weight of the composition.

Silicone Surfactant

The composition of the invention can also optionally comprise a high molecular weight silicone surfactant which can also act as an emulsifier, in place of or in addition to the optional emulsifier(s) already mentioned.

The silicone surfactant is a high molecular weight polymer of dimethyl polysiloxane with polyoxyethylene and/or polyoxypropylene side chains having a molecular weight from 10,000 to 50,000.

The dimethyl polysiloxane polymer is conveniently provided as a dispersion in a volatile siloxane, the dispersion comprising, for example, from 1 to 20% by volume of the polymer and from 80 to 99% by volume of the volatile siloxane. Ideally, the dispersion consists of a 10% by volume of the polymer dispersed in the volatile siloxane.

Examples of the volatile siloxanes in which the polysiloxane polymer can be dispersed include polydimethyl siloxane (pentamer and/or hexamer).

A particularly preferred silicone surfactant is cyclomethicone and dimethicone copolyol, such as DC 3225C Formulation Aid available from DOW CORNING. Another is laurylmethicone copolyol, such as DC Q2-5200, also available from Dow Corning.

The amount of silicone surfactant, when present in the composition will normally be up to 25%, preferably from 0.5 to 15% by weight of the emulsion.

Retinoids

The composition according to the invention optionally can also comprise a retinoid, such as retinoic acid or retinol (Vitamin A) and/or derivative thereof, further to enhance the benefits to skin of the ceramide pathway intermediate.

In addition to retinol itself, examples of derivatives of retinol include:

Retinyl acetate
Retinyl butyrate
Retinyl propionate
Retinyl octanoate
Retinyl laurate
Retinyl palmitate
Retinyl oleate
Retinyl linoleate, and
Retinyl linolenate.

The amount of retinoid, when present in the composition according to the invention is from 0.01 to 10% and preferably 0.1 to 5% by weight of the composition.

Tocopherol

The composition according to the invention optionally can also comprise a tocopherol (vitamin E group), as an antioxidant for the retinoid, when present in the composition, and to limit oxidative damage to skin. The vitamin E group comprises α-tocopherol, β-tocopherol, γ-tocopherol and δ-tocopherol.

The amount of a tocopherol, when present in the composition according to the invention, is from 0.0001 to 20%, preferably from 0.0001 to 10% by weight of the composition.

Water

The composition of the invention can also comprise water, usually up to 90%, preferably from 5 to 80% by volume. Water can function as the cosmetically acceptable vehicle.

OTHER COSMETIC ADJUNCTS

Examples of other cosmetic adjuncts which can optionally be employed in the composition according to the invention include preservatives, such as para-hydroxy benzoate esters; antioxidants, such as butyl hydroxy toluene; humectants, such as glycerol, sorbitol, 2-pyrrolidone-5-carboxylate, dibutylphthalate, gelatin, polyethylene, glycol, preferably PEG 200-600; buffers, such as lactic acid together with a base such as triethanolamine or sodium hydroxide; surfactants, such as glycerol ethers; ceramides of synthetic, animal or plant origin; pseudoceramides; phospholipids; vitamins, such as 1,25 dihydroxy cholecalciferol; waxes, such as beeswax, ozokerite wax, paraffin wax, plant extracts, such as Aloe vera, cornflower, witch hazel, elderflower, cucumber, thickeners; activity enhancers; colourants; perfumes; and sunscreen materials such as ultrafine titanium dioxide and organic sunscreens such as p-aminobenzoic acid and esters thereof, ethylhexyl p-methoxycinnamate, 2-ethoxyethyl p-methoxycinnamate and butyl methoxydibenzoylmethane, and mixtures thereof.

In a further preferred composition, the ceramide pathway intermediate is combined with ceramides, pseudoceramides, polyol fatty acid polyesters, sterols, particularly cholesterol, galactosyldiacyl-glycerols, glycosphingolipids, fatty acids and esters thereof and mixtures thereof and other ingredients, such as mevalonic acid, hexadecylsuccinic acid monobehenyl ester ethoxylate (7.3 EO) and/or derivatives thereof to produce a liposomal

dispersion. Preferred ceramide pathway adjuncts include ceramides, cholesterol, cholesterol pathways intermediates or precursors thereof such as mevalonic acid and fatty acid pathway intermediates or precursors thereof such as acetic acid and malonic acid.

A further preferred composition may also contain in combination with the ceramide pathway intermediate and optional additional ingredients disclosed above, an organic acid component chosen from hydroxy carboxylic acids, such as alpha, beta and omega hydroxyacids, especially glycolic acid, lactic acid and 2-hydroxyoctanoic acid, and keto carboxylic acids, esters thereof and mixtures thereof. It will be appreciated that the invention includes within its scope all enantiomers, diasteromers and mixtures thereof.

In yet another preferred composition, the ceramide pathway intermediate is dissolved in squalene or squalane, optionally together with ceramides and other ingredients, such as mevalonic acid and malonic acid and/or derivatives thereof and formulated with volatile and non-volatile silicones to produce an anhydrous or nearly anhydrous single phase system.

Cosmetic adjuncts can form the balance of the composition.

PRESERVATION OF THE COMPOSITION

The composition according to the invention is preferably preserved in such a manner that it will enjoy an extended shelf life following manufacture and prior to sale and use. Ideally the composition will have an indefinite shelf life.

It is accordingly apparent that the ceramide pathway intermediate is likely to be prone to attack by bacteria, moulds and fungi and other microbial influences, particularly at pH values near that of the skin that characterise the preferred composition. The shelf-life of

the composition can therefore be unacceptably short due to the biodegradation of the precursor unless steps are taken to preserve the composition.

In order to be preserved, the composition should preferably be free, or substantially free, from viable microbial contaminants that are capable of resulting in microbial spoilage of the composition, and/or biodegradation of the precursor prior to topical application of the composition to mammalian skin or hair. It is to be understood, however, that the invention is also concerned with compositions, as herein defined, which may contain viable but dormant microorganisms, such as bacterial spores, provided that the conditions of preservation do not result in substantial proliferation of the microorganisms prior to use of the composition.

Examples of the methods that can be employed to achieve preservation of the composition, includes the following:

(i) Sterilisation

The composition according to the invention can be preserved by sterilisation to remove or kill substantially all viable microbial contaminants. This can be achieved for example by irradiation using a lethal dose of gamma rays, by heat sterilisation or by ultrafiltration using techniques that are well established in the pharmaceutical industry.

(ii) Chemical Preservative

The composition according to the invention can also be preserved by including in it a chemical preservative which functions to prevent the growth of or kill bacteria, fungi or other microorganisms.

Examples of chemical preservatives include ethanol, benzoic

acid, sodium benzoate, sorbic acid, potassium sorbate, sodium propionate and the methyl, ethyl, propyl and butyl esters of p-hydroxybenzoic acid. The amount of chemical preservative that can be incorporated in the composition according to the invention will generally be from 0.05 to 5%, preferably from 0.1 to 2% by weight, the amount chosen being sufficient to arrest microbial proliferation.

(iii) Water activity depressants

The composition according to the invention can also be preserved by the inclusion of a water activity depressant such as glycerol, propylene glycol, sorbitol, sugars and salts, for examples alkali metal halides sulphates and carboxylates. When employing a water activity depressant, sufficient should be incorporated in the composition according to the invention to reduce the water activity (α_w) from 1 to < 0.9, preferably to < 0.85 and most preferably < 0.8, the lowest of these values being that at which yeasts, moulds and fungi will not proliferate.

PROCESS

The invention also provides a process for preparing a composition according to the invention which comprises the steps of mixing an effective amount of a ceramide pathway intermediate, as herein defined, together with a cosmetically acceptable carrier for the intermediate.

USE OF THE COMPOSITION

The composition according to the invention is intended primarily as a product for topical application to human skin, for maintaining or enhancing the skin barrier function, particularly by stimulating the synthesis of ceramides. The composition is particularly useful for treating dry, ageing or damaged skin to reduce moisture

loss, increase stratum corneum flexibility and to enhance the quality of skin. The composition can also be applied to the hair or nails.

In use, a small quantity of the composition, for example from 1 to 5ml, is applied to exposed areas of the skin, hair or nails, from a suitable container or applicator and, if necessary, it is then spread over and/or rubbed into the area to be treated using the hand or fingers or a suitable device.

PRODUCT FORM AND PACKAGING

The topical skin and/or hair and/or nail treatment composition of the invention can be formulated as a lotion having a viscosity of from 4,000 to 10,000 mPas, a fluid cream having a viscosity of from 10,000 to 20,000 mPas or a cream having a viscosity of from 20,000 to 100,000 mPas, or above. The composition can be packaged in a suitable container to suit its viscosity and intended use by the consumer.

For example, a lotion or fluid cream can be packaged in a bottle or a roll-ball applicator or a propellant-driven aerosol device or a container fitted with a pump suitable for finger operation. When the composition is a cream, it can simply be stored in a non-deformable bottle or squeeze container, such as a tube or a lidded jar.

The invention accordingly also provides a closed container containing a cosmetically acceptable composition as herein defined.

EVIDENCE OF EPIDERMAL LIPID (CERAMIDE) BIOSYNTHESIS

The biosynthesis of epidermal lipid, especially ceramides, can be determined by the method described below.

Results of ceramide biosynthesis from sphingosine as the ceramide pathway intermediate are also given.

In-vitro measurement of epidermal lipid biosynthesis

The stimulatory effect of ceramide pathway intermediates (CPI) on lipid levels in the epidermis can be quantified by in-vitro measurements of the level of incorporation of radiolabelled lipid precursors into epidermal lipids over relatively short periods of time (24 hours).

1. Method

Punch biopsies (6mm) were taken of full thickness skin scraped free of subcutaneous fat, and floated dermis side downwards onto 3ml of culture medium (MCDB 153 without animal sera, growth factors, or hormones ex Sigma Chemical Co.), containing radiolabelled lipid precursor (4μCi/ml of 1-14C acetic acid, sodium salt, 7.4 MBq/ml ex Amersham) and CPI (in 96% v/v ethanol vehicle). Following a 24 hour incubation at 37C in air (Harvard/LTE incubator), epidermis was isolated from the dermis by incubation in 10mM ethylenediaminetetraacetic acid solution at 37C for 30 minutes, and placed into 3ml of chloroform:methanol (2:1 v/v) solution for lipid extraction. After 18 hours 0.75ml of potassium chloride solution (0.88% w/v) was added with mixing which after centrifugation produced 2 liquid phases, an upper aqueous phase, and a lower organic phase containing the lipids. Beckman ReadySafe scintillation fluid (4ml) was added to 100μl aliquots of the organic phase and counted in a Beckman LS 6000IC scintillation counter to determine the radioactivity present in the lipids.

Subsequently 1ml aliquots of the organic phase were evaporated to dryness under nitrogen, redissolved in 100μl of chloroform:methanol (2:1 v/v), and transferred to a high

performance thin layer chromotography plate (HPTLC, silica gel 60, 10x20 cm ex Merck). To resolve the various lipid classes, the plate was run successively with i) chloroform:methanol:acetone (76:20:4) to 15 and then 30mm, ii) chloroform:methanol:acetone (79:12.5:8.5) to 80mm, and finally iii) chloroform:ethyl acetate:diethyl ether:methanol (72:20:6:2) to 95mm. After drying at 120C the plate was saturated with 15ml of acidic copper sulphate solution (10% copper sulphate, 8% phosphoric acid) for 1 minute and then the lipids charred by heating to 120C for 1 minute and then 160C for 10 minutes. Lipid bands were identified using authentic lipid standards (Sigma Chemical Co.) and were quantified by reflectance densitometric scanning at 420nm using a Shimadzu CS-9000 flying spot densitometer. Plates were then placed onto X-ray film (Amersham Multipurpose MP) in cassettes with intensifying screens and exposed for 1 to 4 weeks. Films were developed with a Fuji RGII X-ray film processor and bands quantified by transmission densitometric scanning at 530nm using a Shimadzu CS-9000 flying spot densitometer.

Specific activity was calculated by dividing the radioactivity in each band by the mass of lipid in each band. Each lipid class was identified using authentic lipid standards.

2. Statistical Analysis

Mean values were compared using Students t test and significance was set at the 5% level.

3. Results

The effect of the CPI, sphingosine, on epidermal lipid biosynthesis on three separate occasions: (Experiments A, B & C), is shown in Figure 2. An increase in the level of radiolabelled acetate incorporated into epidermal lipids

was evident when sphingosine (SPH) was present in the medium at a level of 0.08mM, producing a consistent 20-25% increase over control (C, incubated without sphingosine) after 24 hours, indicating a reproducible stimulation of epidermal lipid biosynthesis.

The effect of sphingosine on individual lipid classes was determined using HPTLC. For each lipid class examined sphingosine at 0.08mM increased the level of incorporation of radiolabelled acetate in comparison to the control (no sphingosine). The specific activity (radioactivity/lipid mass) for each lipid class and the ratio of sphingosine treated to control is shown in Table 1. The ceramide and glucosylceramide class showed the greatest increase in radioactivity incorporation following sphingosine treatment followed by non-polar lipids and finally phospholipids and cholesterol sulphate.

Table 1 : Effect of sphingosine on the specific activity of various lipid classes

Lipid	Specific Activity (radio activity/mass)		
	Control	Sphingosine	Ratio SPH/C
Non-polar	0.031(0.017)	0.066(0.059)	2.13
Ceramide	0.0085(0.0044)	0.029(0.028	3.40
Glucosylceramide	0.045(0.024)	0.136(0.140)	3.02
Chol. sulphate	0.297(0.0762)	0.424(0.150)	1.43
Phospholipid	0.264(0.105)	0.412(0.193)	1.56

Data shown as Mean (standard deviation), n=4 for control and sphingosine treated.

4. Conclusions

Sphingosine stimulates epidermal lipid biosynthesis,

increasing the synthesis of all the lipid classes examined, but particularly the glucosylceramide and ceramide class.

Effect of ceramide percursors on keratinocyte glucosylceramide synthesis

1. Method

Human keratinocytes (ex clonetics were seeded in 6 well plates and allowed to reach 80% confluency after incubation in Keratinocyte Growth Medium (KGM ex clonetics, 0.15mM calcium) at 37C, 5% CO2. Fresh medium was added containing radiolabelled lipid precursor (2μCi/ml of 1-14C acetic acid, sodium salt, 7.4 MBq/ml ex Amersham) and CPI (in 96% v/v ethanol vehicle) and incubated for 24 hours as above. Cells were harvested by scraping, lyophilized, and lipids extracted using 3ml of chloroform:methanol solution (2:1 v/v) as above. Scintiverse BD scintillation fluid (10ml ex Fisher) was added to 100μl aliqouts of the organic phase and counted in a Beckman LS 6000 IC Scintillation counter to determine the radioactivity present in the lipids.

Subsequently, 200μl aliqouts of the organic phase were applied to 1cc aminopropyl-silica columns (ex Walters) and lipid fractions eluted by successive washes of hexane, chloroform:isopropanol (2:1 v/v), and acetic acid (2% v/v) in methanol. Radioactivity in each fraction was determined as above and compared to the total radioactivity of all the lipids. Furthermore fractions were evaporated to dryness, redissolved in 20ul of chloroform:isopropanol (2:1 v/v) and lipid species present in each fraction identified by high performance thin layer chromatography as described in HPTLC for the organ culture experiments.

2. Statistical analysis

Mean values were compared using students t test and

significance was set at the 5% level.

3. Results

The effects of the CPI's sphingosine (SPH), phytosphingosine (PHYT), and tetraacetylphytosphingosine (TAPS) on glucosylceramide synthesis (as identified by HPTLC) is shown in Figure 3. A significant increase above control (no CPI present) over 24 hours in the proportion of radiolabelled acetate incorporated into all lipid was evident when CPI was present in the medium as a level of 0.02mM, indicating a stimulation of keratinocyte glucosylceramide synthesis. Furthermore, TAPS produced a significantly higher proportion of radiolabel incorporated that SPH (Figure 3) indicating that TAPS stimulates the synthesis of glucosylceramide more than SPH. PHYT was more effective that SPH, but less effective than TAPS.

Incorporation of Lipid Precursors into Ceramides/Cerebrosides in Keratinocytes in culture

METHOD

Cell Culture:

Human Keratinocytes were grown to 90% confluency in serum-free Keratinocyte Growth Medium (KGM, Clonetics Corporation, San Diego CA) containing 0.15mM calcium. Cells were incubated with lipid precursors (phytosphingosine, tetraacetylphytosphingosine and juniperic acid) dissolved in ethanol for 24h. Following incubation the cells were harvested in 1.8mL of potassium chloride solution (0.88% w/v), the lipids extracted using chloroform:methanol, and the chloroform layer containing the lipids was anlysed by high performance thin layer chromatography.

Lipid Analysis:

The organic phase was dried under nitrogen, and resuspended in 200μL of chloroform. Different lipid classes were separated based upon their polarity, using aminopropyl column chromatography. 200μL of lipid was eluted with successive washes of hexane, hexane:ethyl acetate (85:15 v/v), and chloroform:isopropanol (2:1 v/v). The fractions were then evaporated to dryness under nitrogen, and resuspended in 100μL of chloroform:methanol (2:1 v/v). 1/3 of the lipid was spotted onto high performance thin layer chromatography (HPTLC) silica gel plates and developed with an appropriate solvent system. Following lipid separation, the plate was dipped in a 10% copper sulphate solution, charred at 165°C for 20 minutes, and quantified via reflectance densitometry.

Results:

Tetra-acetyl phytosphingosine (TAPS) and phytosphingosine (PHYT) and juniperic acid (HA) were examined for their potential to generate phytoceramide 1, a ceramide 1-like molecule. Due to the extra hydroxyl group present on TAPS and PHYT compared with sphingosine the ceramide generated chromatographically migrates between ceramide 1 and 2. As can be seen from the results TAPS and HA produce significant amounts of phytoceramide 1. PHYT and HA, however, produce more of the glucosyl derivatives.

Conclusions:

The combination of a sphingoid-base and an omega hydroxy fatty acid is capable of being used by keratinocytes to generate a ceramide 1-like molecule.

Effect of Ceramide I Precursors on Phytoceramide I Levels

		Phytoceramide I as % of total lipid	Standard Deviation
1	Control	0.881	0.048
2	HA	0.816	0.125
3	PHYT	0.659 **	0.113
4	HA+PHYT	0.357 *	0.070
5	TAPS	1.310 **	0.204
6	HA+TAPS	3.896 **	0.863

* $P < 0.1$

** $P < 0.5$

		Glucosylceramide I as % of total lipid	Standard Deviation
1	Control	1.340	0.527
2	HA	1.526	0.284
3	PHYT	4.217 *	1.000
4	HA+PHYT	5.417 *	0.900
5	TAPS	4.424 *	0.535
6	HA+TAPS	1.577	0.493

* $P \leq 0.05$

CLINICAL STUDIES

1. Stratum corneum ceramide levels following topical TAPS treatment

In a one-month clinical study on 10 subjects, a 1% solution of tetraacetylphytosphinosine (TAPS) in an

ethanol/propylene glycol (1:1) vehicle was applied to the volar forearm twice daily; an adjacent site on the forearm was treated with vehicle alone. The dosage amount was 100μl applied to approximately 35 sq cm. After one month of treatment, a skin surface biopsy was taken from each site by tape-stripping with sellotape polyester tape. Each 'biopsy' consisted of eight consecutive tape strips of 2x3 cm each. Stratum corneum material was released from the tape by sonication in methanol, the methanol was dried off, and lipids were extracted in 2:1 chloroform:methanol. Solid phase extraction columns were used for preliminary lipid separation, followed by high performance thin layer chromatography (HPTLC) and densitometry for ceramide quantitation. The delipidized squames were incubated in protein extraction buffer, and protein content was determined by Pierce BCA assay.

ng Ceramide/μg Protein			
Subject	Vehicle-treated	TAPS-treated	Change
1	34.42	45.21	+
2	36.22	42.09	+
3	59.16	90.61	+
4	44.27	48.02	+
5	25.96	43.31	+
6	44.10	52.51	+
7	52.66	59.85	+
8	80.26	42.20	-
9	75.81	56.43	-
10	40.56	27.82	-
Mean	49.3	50.8	
S.D.	17.8	16.6	

Paired t-test: Means not significantly different

Subjects showing increased ceramide levels following TAPS treatment (N=7):

Treatment	ng Lipid/ug Protein		
	Ceramide	Cholesterol	Fatty Acid
TAPS	54.5 (17.1)	24.2 (10.1)	75.0 (49.1)
Vehicle	42.4 (11.3)	18.5 (4.4)	55.7 (21.1)
Paired t-test	p=0.015	n.s.d.	n.s.d.

Conclusions

These results show that TAPS improves the levels of ceramides in the stratum corneum but has no effect on cholesterol and fatty acid levels, indicating its specificity as a ceramide precursor.

EXAMPLES

The invention is illustrated by the following examples.

Example 1

This example illustrates a high internal phase water-in-oil emulsion.

A high internal phase water-in-oil emulsion having the following formulation was prepared:

	% w/w
Fully hydrogenated coconut oil	3.9
phytosphingosine	0.1
Brij 92*	5
Bentone 38	0.5
Preservative	0.3
$MgSO_4 7H_2O$	0.3
Butylated hydroxy toluene	0.01
Perfume	qs
Water	to 100

*Brij 92 is polyoxyethylene (2) oleyl ether

Example 2

This example also illustrates a high internal phase water-in-oil emulsion in which the formulation of Example 1 was prepared but with the following changes:

i. liquid paraffin replaced the fully hydrogenated coconut oil, and

ii. partially esterified phytosphingosine having the structure (11), replaced phytosphingosine per se.

Example 3

This example also illustrates a high internal phase water-in-oil emulsion in which the formulation of Example 1 was prepared, except that sphingosine replaced phytosphingosine per se.

Example 4

This example illustrates an oil-in-water cream.

An oil-in-water cream emulsion having the following formulation was prepared:

	% w/w
Mineral oil	4
Sphingosine derivative having the structure (8)	0.1
Brij 56*	4
Alfol 16RD*	4
Triethanolamine	0.75
Butane-1,3-diol	3
Xanthan gum	0.3
Preservative	0.4
Perfume	qs
Butylated hydroxy toluene	0.01
Water	to 100

*Brij 56 is cetyl alcohol POE (10)
Alfol 16RD is cetyl alcohol

Example 5

This example also illustrates an oil-in-water emulsion, in which the formulation of example 4 was prepared, except that the sphinganine derivative having the structure (5) replaced the sphingosine derivative having the structure (8).

Example 6

This example also illustrates an oil-in-water emulsion in which the formulation of example 4 was prepared, except that sphinganine replaced the sphingosine derivative having the structure (8).

Example 7

This example illustrates an alcoholic lotion according to the invention.

The lotion had the following formulation:

	% w/w
Phytosphingosine derivative having the structure (10)	0.2
Ethanol	40
Perfume	qs
Butylated hydroxy toluene	0.01
Water	to 100

Example 8

This example illustrates an alcoholic lotion containing a sphingosine derivative of the invention.

The lotion had the following formulations:

	% w/w
Sphingosine derivative having the structure (6)	0.2
Dimethylsulphoxide	10
Ethanol	40
Antioxidant	0.1
Perfume	qs
Water	to 100

Examples 9 and 10

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

	% w/w	
	9	10
phytosphingosine	1.5	-
Sphingosine having the structure (7)		0.5
Perfume	0.1	0.1
Hydroxyethyl cellulose	0.4	0.4
Absolute ethanol	25	25
p-methyl benzoate	0.2	0.2
Sterilised demineralised water	to 100	to 100

Examples 11 and 12

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

	% w/w	
	11	12
sphinganine derivative having the structure (4)	0.08	-
sphinganine	-	0.15
Ethanol	10	10
Perfume	0.5	0.5
Distilled water	to 100	to 100

Example 13

This example illustrates a high internal phase water-in-oil emulsion.

A high internal phase water-in-oil emulsion having the following formulation was prepared:

	% w/w
Fully hydrogenated coconut oil	3.9
tetraacetyl phytosphingosine (Structure 2)	0.1
Brij 92*	5
Bentone 38	0.5
Preservative	0.3
$MgSO_4 7H_2O$	0.3
Butylated hydroxy toluene	0.01
Perfume	qs
Water	to 100

*Brij 92 is polyoxyethylene (2) oleyl ether

Example 14

This example illustrates an oil-in-water cream.

An oil-in-water cream emulsion having the following formulation was prepared:

	% w/w
Mineral oil	4
Sphingosine	0.2
Phytosphingosine	0.1
Brij 56*	4
Alfol 16RD*	4
Triethanolamine	0.75
Butane-1,3-diol	3
Xanthan gum	0.3
Preservative	0.4
Perfume	qs
Butylated hydroxy toluene	0.01
Water	to 100

*Brij 56 is cetyl alcohol POE (10)
Alfol 16RD is cetyl alcohol

Example 15

This example illustrates an alcoholic lotion.

The lotion had the following formulation:

	% w/w
Tetraacetyl phytosphingosine	0.5
Sphingosine	0.2
Ethanol	40
Perfume	qs
Butylated hydroxy toluene	0.01
Water	to 100

Example 16

This example illustrates an alcoholic lotion containing a sphinganine derivative of the invention.

The lotion had the following formulations:

	% w/w
Sphinganine derivative having the structure (3)	0.2
Dimethylsulphoxide	10
Ethanol	40
Antioxidant	0.1
Perfume	qs
Water	to 100

Examples 17 and 18

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

	% w/w
N-acetyl phytosphingosine (Structure 9)	1.5
Perfume	0.1
Hydroxyethyl cellulose	0.4
Absolute ethanol	25
p-methyl benzoate	0.2
Sterilised demineralised water	to 100

CLAIMS

1. A composition suitable for topical application to human skin which comprises:

(i) from 0.0001 to 10% by weight of one or more ceramide pathway intermediates or precursors thereof or mixtures thereof; and

(ii) a balancing amount of a cosmetically acceptable vehicle for the intermediate.

2. A composition according to claim 1, in which the ceramide pathway intermediate or precursor thereof comprises sphinganine, sphingosine or phytosphingosine or a N-acyl, O-acyl or N-alkyl derivative thereof or mixture thereof.

3. A composition according to claim 1 or 2, in which the ceramide pathway intermediate precursor comprises N-methyl sphinganine or N,N'-dimethyl sphinganine.

4. A composition according to claim 1 or 2, in which the ceramide pathway intermediate precursor comprises N-methyl sphingosine or N,N'-dimethyl sphingosine.

5. A composition according to claim 1 or 2, in which the ceramide pathway intermediate precursor comprises N-methyl phytosphingosine or N,N'-dimethyl phytosphingosine.

6. A composition according to claim 1 or 2, in which the ceramide pathway intermediate comprises tetraacetyl phytosphingosine.

7. A composition according to claim 1, in which the ceramide pathway precursor comprises serine or palmitoyl CoA.

8. A composition according to any preceding claim in which the ceramide pathway precursor forms from 0.01 to 5% by weight of the composition.

9. A composition according to any preceding claim which further comprises a ceramide pathway adjunct chosen from saturated or unsaturated alpha-, beta- or omega hydroxy fatty acids, ceramides, cholesterol, cholesterol pathway intermediates or precursors thereof, fatty acid pathway intermediates or precursors thereof or mixtures thereof.

10. A method of treating skin, particularly dry or damaged skin, which comprises the step of contacting the skin topically with a ceramide pathway intermediate or a precursor thereof according to claim 1.

11. The use of a ceramide pathway intermediate or a precursor thereof in accordance with claim 1, in maintaining or enhancing the skin barrier function.

12. The use of a ceramide pathway intermediate or a precursor thereof in the treatment of skin to reduce or delay development of wrinkling associated with advancing age, or with sun-induced skin ageing.

Figure 1

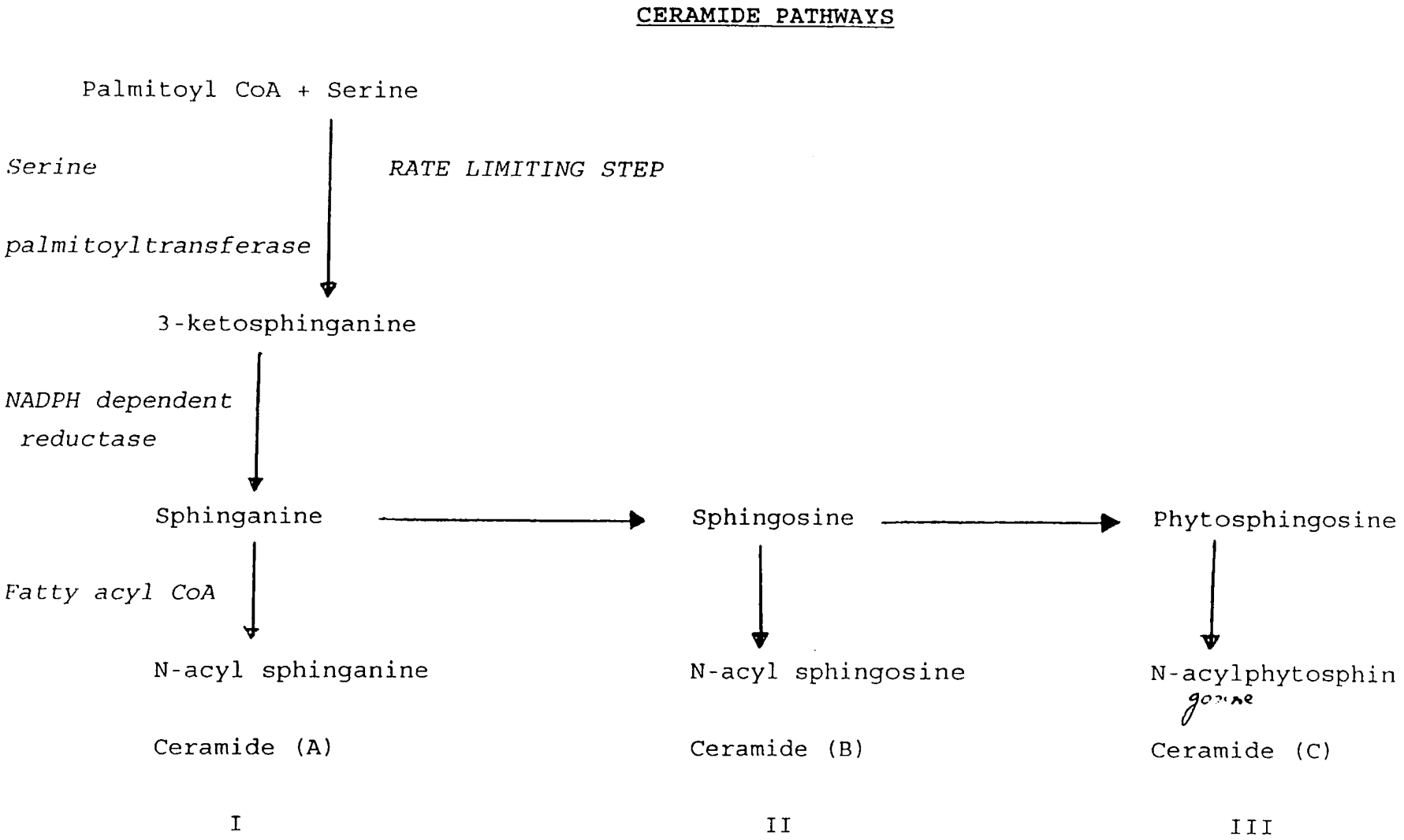

CERAMIDE PATHWAYS
Palmitoyl CoA + Serine
Serine
RATE LIMITING STEP
palmitoyltransferase
3-ketosphinganine
NADPH dependent
reductase
Sphinganine
Sphingosine
Phytosphingosine
Fatty acyl CoA
N-acyl sphinganine
N-acyl sphingosine
N-acylphytosphingosine
Ceramide (A)
Ceramide (B)
Ceramide (C)
I
II
III

Fig.2

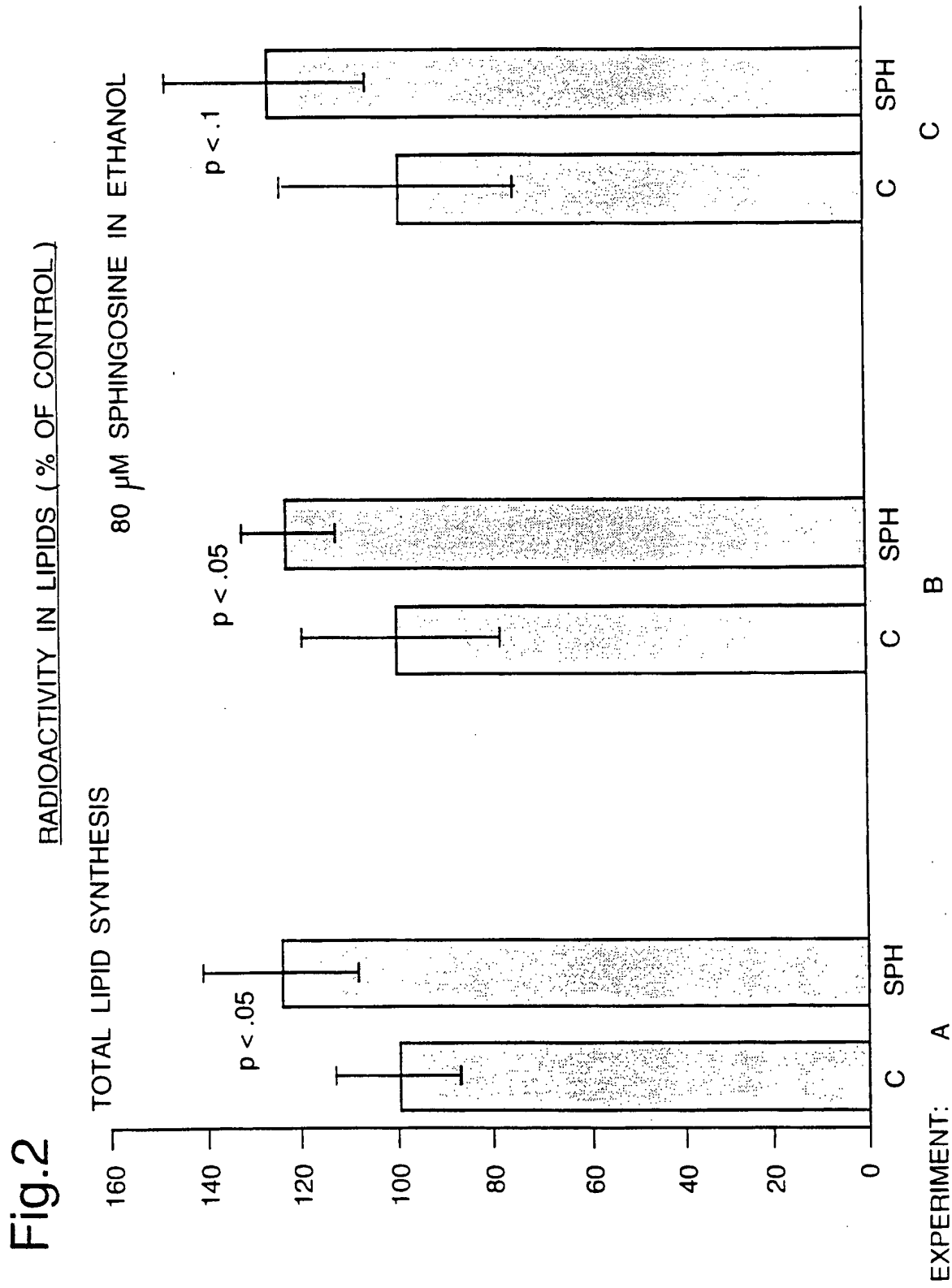
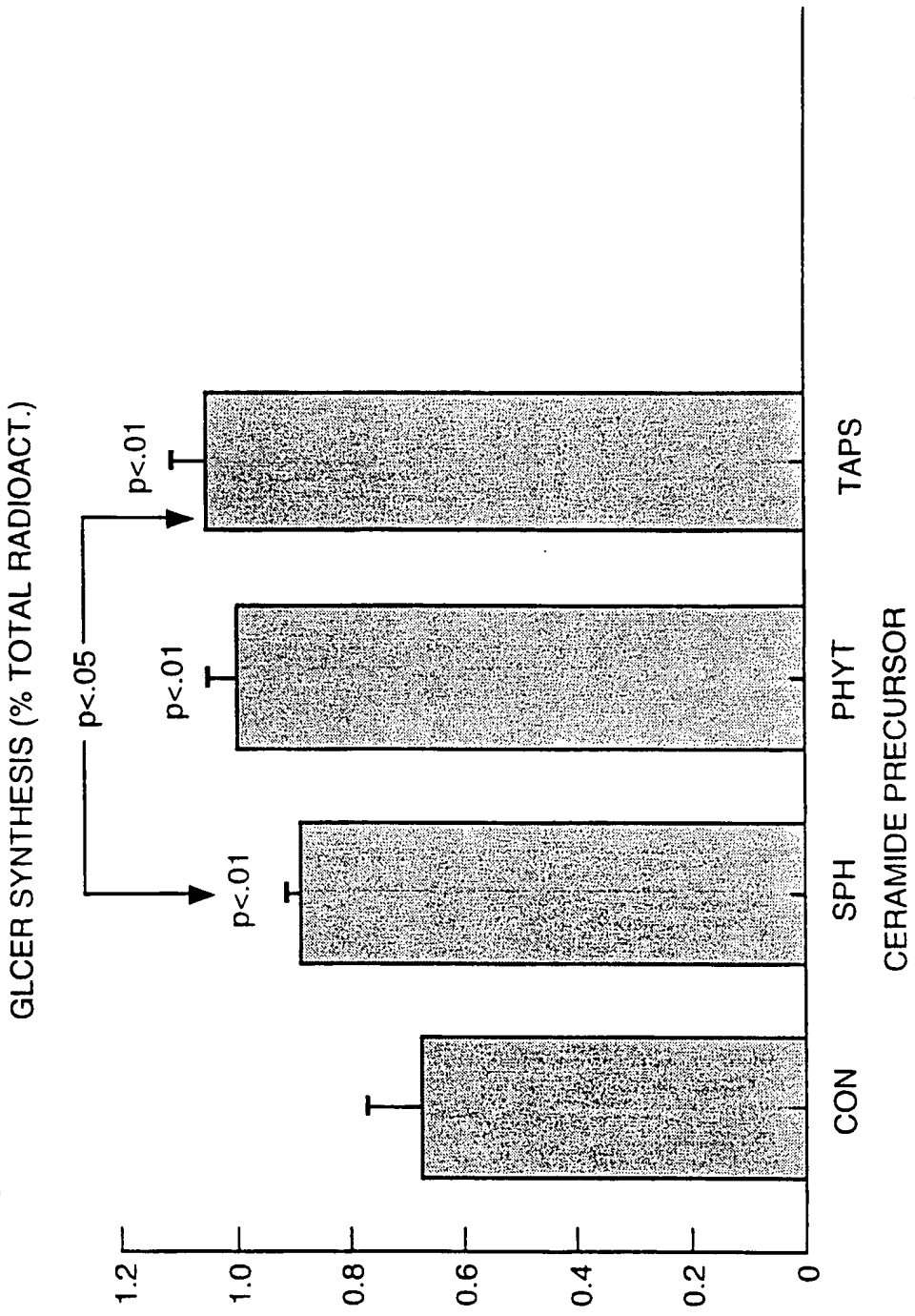

RADIOACTIVITY IN LIPIDS (% OF CONTROL)
TOTAL LIPID SYNTHESIS
80 μM SPHINGOSINE IN ETHANOL
160
140
120
100
80
60
40
20
0
p < .05
p < .05
p < .1
C
SPH
C
SPH
C
SPH
EXPERIMENT: A
B
C

Fig.3.


GLCER SYNTHESIS (% TOTAL RADIOACT.)
1.2
1.0
0.8
0.6
0.4
0.2
0
p<.05
p<.01
p<.01
p<.01
CON
SPH
PHYT
TAPS
CERAMIDE PRECURSOR

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR,A,2 654 618 (SEDERMA) 24 May 1991 see page 3, line 4 - line 8 see page 3, line 16 - line 20 see claim 1	1,2,4,12
P,X	FR,A,2 692 781 (SEDERMA) 31 December 1993 see the whole document	1,8, 10-12
X	WO,A,88 06034 (M.G. FIASCHETTI) 25 August 1988 see page 4 see page 5, line 1 - line 19 see page 6, line 31 - line 34 see page 7 see claims 1,6,8	1,7, 10-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 August 1994	16.08.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Sierra Gonzalez, M

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-2654618	24-05-91	NONE	
FR-A-2692781	31-12-93	NONE	
WO-A-8806034	25-08-88	US-A- 4885157	05-12-89